

(19)



Europäisches Patentamt
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Office européen des brevets



(11)

EP 0 875 218 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
16.02.2005 Bulletin 2005/07

(51) Int Cl.⁷: **A61F 2/06, A61L 31/00**

(21) Application number: **98302905.9**

(22) Date of filing: **15.04.1998**

(54) **Porous medicated stent**

Wirkstoffhaltige poröse Metallprothesen

Prothèses métalliques poreuses renfermant des substances actives

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL

(30) Priority: **15.04.1997 US 842660**

(43) Date of publication of application:
04.11.1998 Bulletin 1998/45

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Description

[0001] This invention generally relates to a medicated prosthesis or implant. More particularly, the invention relates to a medicated intra-vascular stent, that is radially expandable in the vasculature of a patient and delivers a therapeutic agent to the site of the implantation.

[0002] Stents are generally cylindrically-shaped prosthetic implants which function to hold open and sometimes expand a segment of a blood vessel or other anatomical lumen. They are particularly suitable for supporting and preventing a torn or injured arterial lining from occluding a fluid passageway. Intravascular stents increasingly are useful for treatment of coronary artery stenoses, and for reducing the likelihood of the development of restenosis or closure after balloon angioplasty.

[0003] The success of a stent can be assessed by evaluating a number of factors, such as thrombosis; neointimal hyperplasia, smooth muscle cell migration and proliferation following implantation of the stent; injury to the artery wall; overall loss of luminal patency; stent diameter in vivo; thickness of the stent; and leukocyte adhesion to the luminal lining of stented arteries. However, the chief areas of concern are early subacute thrombosis, and eventual restenosis of the blood vessel due to intimal hyperplasia.

[0004] Therapeutic pharmacological agents have been developed to improve successful placement of the stent and are delivered to the site of stent implantation. Stents that are of a common metallic structure were previously unable to deliver localized therapeutic pharmacological agents to a blood vessel at the location being treated with the stent. There are polymeric materials that can be loaded with therapeutic agents including drugs or other pharmacological treatments which agents then can be released for drug delivery. However, these polymeric materials may not fulfil the structural and mechanical requirements of a stent, especially when the polymeric materials are loaded with a drug, since drug loading of a polymeric material can significantly reduce the structural and mechanical properties of the polymeric material.

[0005] WO 94/13268 discloses a stent having a delivery matrix which provides for the controlled release of bioactive substances. The delivery matrices comprise porous and erodible filaments, and multiple filaments may be employed in order to release different bioactive substances at different delivery rates.

[0006] It has been known in the art to coat a metallic stent with a polymeric material and to load the polymeric material with a drug. Alternatively, stents of polymeric materials have been reinforced with metal structure. These stent designs have the strength necessary to hold open the lumen of the vessel because of the reinforcement contributed by the metal. Stents made of polymeric material and metal have a larger radial profile because the volume occupied by the metal portion of

the stent cannot absorb and retain drugs. Reducing the profile of a stent is desirable because doing so increases the in vivo diameter of the lumen created by the stent. Thus it is desirable to configure a metallic stent to deliver drugs to the blood vessel walls without substantially increasing the profile of the stent.

[0007] According to the present invention there is provided a metallic stent configured to maintain patency of a human vessel, the stent having a plurality of pores; a therapeutic medication loaded into the pores of the metallic stent; and a polymeric coating over the surface of the stent wherein the medication in the pores of the stent is a first medication and wherein the coating contains a second medication.

[0008] The implantable stent has pores or porous cavities in the metallic portion of the prosthesis so that therapeutic agents such as drugs can be loaded directly into the pores without substantially weakening the structural and mechanical characteristics of the prosthesis. The stent of the present invention can be implanted at a specific site of vascular injury, such as can result from balloon angioplasty or *de novo* lesions of atherosclerotic disease. The drugs in the pores of the stent can treat restenosis and tissue inflammation, and promote endothelialization or any other disease or condition that might detract from the success of a stent implantation.

[0009] Advantageously, the pores of the stent can be formed by sintering the stent material from the metallic particles, filaments, fibres or other materials. The stent can be formed from a sintered wire that is coiled or otherwise is formed into a stent. The stent can be formed from a sintered cylindrical tube or sintered metal sheet which can be laser-cut or chemically etched into an expandable stent structure.

[0010] Additionally, the porosity of the stent metal can be increased by using particles that are not generally spherical such as fibrous particles, filaments or wires. Advantageously, the interwoven fibers and filaments also can be sintered after they have been woven into the desired shape.

[0011] Advantageously, the stent is formed from a metal wire or strut that is comprised of a first layer of particles, oriented along a first axis, which forms a core, and an outer layer of particles that are arranged radially outward from the inner layer of particles. The particles in the outer layer have a smaller diameter than the particles in the inner layer. The core permits a greater volume of drugs in the center of the stent. The smaller diameter particles on the outside control the rate at which drugs are released into the walls of the vessel. The larger diameter particles result in a layer of greater porosity which thus is capable of carrying a higher volume of medication.

[0012] It may be desirable to form a stent that has a solid core and a porous outer section. This can be accomplished by sintering particles to a solid, non-porous, metal wire. A stent so configured has a solid core which reinforces the structure of the stent and thereby adds

strength to the device. The porous particles sintered to the surface of the stent absorb drugs for delivery.

[0013] The stent may be formed from a sheet or tube of sintered metal. The sheet or tube is cut according to a pattern that allows the stent to be expanded and thus deployed into the vasculature. The stent pattern of this embodiment can be stenciled onto the sheet or tube of sintered metal and then may be cut by laser-cutting the sheet into the desired shape. Alternatively, the stent can be chemically etched into its desired shape.

[0014] In certain applications, it is desirable that the coating be biopolymer and in other applications, the coating preferably is a synthetic polymer or a hydrogel. The coating also can be a heparin coating that is affixed to the surface of the stent through ionic bonding, end-point attaching or photolinking the heparin.

[0015] Advantageously, the coating preferably is permeable to the medication. The permeability of the coating should be selected to release the medication in the stent at a desired rate.

[0016] Advantageously, a bioabsorbable coating is applied to the stent. This coating is dissolved by the body fluids. According to one application, the coating preferably is loaded with the same drug or medication that is loaded into the stent. In another embodiment, the coating is loaded with a medication that is different than that which is carried by the stent. In this configuration, the two medications are released sequentially.

[0017] It is also desirable to provide a method of using a medicated prosthesis, the method comprising providing a porous prosthesis, loading a drug into the pores of the prosthesis, positioning the prosthesis in an appropriate site and affixing the prosthesis to the site. The method further includes the step of applying a coating to the stent after the step of loading the drug.

[0018] These and other features of the present invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the present invention.

FIGURE 1 is a longitudinal sectional view of a blood vessel with a stent.

FIG. 2 is a porous stent wire or strut in a partially magnified, partially cut-away perspective view.

FIG. 3 is a magnified, cross-sectional view of unsintered, packed particle.

FIG. 4 is a porous stent wire or strut in a partially magnified, partially cut-away perspective view. invention.

FIG. 5 is a porous stent wire or strut in a partially magnified, partially cut-away perspective view.

FIG. 6 is a cross-sectional view of a stent wire or

strut.

FIG. 7 is a cross-sectional view of a stent wire or strut.

FIG. 8 shows a sheet of sintered stent.

FIG. 9 shows a stent formed from a sheet of sintered metal.

FIG. 10 is a cross-sectional, partially cut-away view of a sheet of sintered metal.

FIG. 11 is a cross-sectional view of a stent wire or strut

FIG. 12 is a cross-sectional view, partially cut-away of a sheet of sintered metal .

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0019] Referring to FIGURE 1, the prosthesis of one arrangement a porous stent 12 that is radially expandable against the walls 14 of a vessel 16. A therapeutic agent is loaded into the pores 18 (See FIG. 2) of the stent. When placed in the vasculature, the therapeutic agent is delivered to the tissue that comes into contact with the stent. The stent may be formed of a stent wire that is porous. An example of a porous stent wire is a sintered metal wire. FIG. 2 illustrates a partial microscopic view of a sintered wire that is suitable for use in a stent. The wire is porous and has several pores 18. The cavities preferably range in size between 0.01 and 20 microns.

[0020] The metal may be made porous by the process of sintering metal. Sintering is a process of fabrication where particles are bonded together to form a coherent mass without entirely melting the particles. Particles are pressed together or molded into a desired shape. A considerable amount of pressure first is applied to press the particles together. Then the metal is heated to temperatures slightly below the melting point of the metal. Without entirely melting, the particles bond to each other. Space remains between the lattice of the particles and this space defines the pores 18.

[0021] The formation of sintered metal is illustrated with reference to FIG. 3 and continued reference to FIG. 2. FIG. 3 is a microscopic view of a packed lattice 22 of metallic particles 24. Gaps 26 exist between each particle despite the fact that the particles are pressurized and are in contact with adjacent particles. Particles preferably are sized between 0.02 microns and 20 microns in diameter. Prior to heating, there are no chemical bonds formed between the individual particles. When the metal is heated to slightly below the melting point of the metal, the particles bond with neighboring particles. The gaps in the packed lattice form pores 18 when the

particles are sintered. Thus in FIG. 2, the metal stent wire formed by the process of sintering has pores 18 extending throughout the entire wire, thereby interconnecting the cavities. The cavities then can be filled with a therapeutic agent as hereinafter described. The appropriate pressure and temperature of sintering a particular metal is specific to that particular metal. One skilled in the art of metal fabrication would understand how to sinter any given metal or alloy.

[0022] A metal stent material member can be a suitable metal such as stainless steel, tantalum, nickel-titanium alloy, platinum-iridium alloy, molybdenum-rhenium alloy, gold, magnesium, combinations thereof, although other similar materials also may be suitable. The metal can be modified to exhibit different hardnesses, and thus varying stiffnesses, by well known annealing and manufacturing processes.

[0023] One of the factors to be considered when making a stent is the porosity of the metal. Porosity is the total volume of pores in the sintered metal divided by the total volume of the metal. Porosity determines the amount of a therapeutic agent that can be loaded into a stent of predetermined dimensions. High porosity means that a stent can deliver more therapeutic agents or have a narrower profile because it is less dense. High porosity, may adversely affects the strength and elasticity of a metal. Consequently, there is an ongoing tradeoff between stent strength, on the one hand, and stent profile and stent load capacity on the other hand.

[0024] Pore size is a function of the size of the particles which create the gaps that establish the pores. In FIG. 3, the particles 24 generally are spherical. The size of each pore 18 is proportional to particle size, particularly with generally spherical particles. When the particles 24 are not of uniform size, smaller particles tend to fill the gaps between larger particles. Thus, the porosity of the metal formed with such particles is less predictable than when more equally-sized particles are used. General uniformity of pore size also is important to ensure that drugs are dispersed evenly throughout the stent. A generally uniform distribution of pores insures that the tissue in contact with the stent will receive an evenly distributed dose of a therapeutic agent.

[0025] There are several types of drugs that currently are administered at the site that a stent is placed in the vessel. Examples of therapeutic drugs, or agents that can be combined with the particle layers, include antiplatelets, anticoagulants, antifibrins, antithrombins and antiproliferatives. Examples of antiplatelets, anticoagulants, antifibrins and antithrombins include but are not limited to sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and an antiplatelet drug sold under the trademark "7E-3B" by Centocor, Inc. Examples of

cytostatic or antiproliferative agents include angiotensin, a somatostatin analogue; angiotensin-converting enzyme inhibitors, such as those manufactured under the trademarks "Captopril" (by Squibb Corp.), "Cilazapril" (by Hoffman-LaRoche, Inc.) and "Lisinopril" (by Merck & Co., Inc.); calcium channel blockers such as nifedipine; colchicine; fibroblast growth factor (FGF) antagonists; fish oils, such as omega 3 fatty acids; cholesterol-lowering drugs such as inhibitors of HMG-CoA reductase, one of which is sold under the trademark "Lovastatin" by Merck & Co., Inc.; methotrexate, monoclonal phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glaxo Wellcome, Inc., PDGF antagonists such as seramin and triazopyrimidine, serotonin blockers, steroids, thioprotease inhibitors, and nitric oxide. Other therapeutic drugs which may be appropriate include alpha-interferon and genetically-engineered epithelial cells, for example.

[0026] The foregoing therapeutic agents have been used to prevent or to treat restenosis, and each is identified by way of example and not by limitation, as other therapeutic drugs may be developed which equally are applicable for use with the present invention. Using such therapeutic agents to treat vessels or body lumens is known in the art, as is the calculation of dosages, dosage rates and appropriate duration of treatment.

[0027] The therapeutic agent may be in liquid form and is loaded into a stent by immersing the stent in a medicated solution. The therapeutic agent may be dissolved in a solvent or suspended in a liquid mixture. If a suspension is used, it is important that the pore size of the stent is considerably larger than the suspended particles of the therapeutic agent. An average pore size that is more than ten (10) times the particle size of a suspended therapeutic agent is suitable. After the stent is immersed in the medicated solution, the therapeutic agent is absorbed into the pores of the stent. The loaded stent then can be removed from the solution and implanted into the vasculature of a patient. Optionally, the loading of the therapeutic agent into the stent can be facilitated by applying pressure to the fluid in which the agent is dissolved or suspended. The applied pressure will aid the passage of medicated fluid into the pores of the stent. This technique might be likened to the physical process of forcing a fluid through the pores of a filter.

[0028] Once loaded into the stent the therapeutic agent remains in place by reason of the surface tension between the outer surfaces of the particles that form the pores 18 and the particles of the therapeutic agent. As shown in FIG. 1, the loaded or medicated porous stent 12 then is deployed to the site of an arterial closure 13 and is expanded. The expanded stent engages the walls 14 of the vessel 16 to maintain the patency of the vessel. Once in the vessel and as is illustrated in FIG. 2, the therapeutic agent disseminates from the pores 18 and is absorbed into the tissue of the walls of the vessel that are in contact with the stent.

[0029] Among the advantages of a stent embodying

the present invention over prior art medicated stents are its profile and strength. Metal, including sintered metal, is stronger than synthetic materials, such as polymer blends, which are capable of being loaded with a therapeutic agent. Thus, in order for a medicated stent to deliver an appropriate amount of a therapeutic agent and structurally maintain vessel patency, the radial profile of the stent must be substantially larger than that of metal stents. This is true whether or not a metal stent is coated with a polymeric material to carry a therapeutic agent, or if the stent is made entirely of a plastic material.

[0030] Sintered metal has strength and elasticity that is comparable to non-sintered metal. Sintered metal further has the added feature of porosity. Consequently, a sintered metal stent can be manufactured with a profile that is substantially comparable to that of a conventional metal stent, and a therapeutic agent can be loaded into the pores and delivered to the site of stent implantation without the aid of medicated polymer coatings.

[0031] Additionally, many synthetic materials, including materials that are bioabsorbable, can cause inflammation of the tissue. A medicated metal stent having a therapeutic agent loaded directly into the pores of the stent likely will be less apt to cause irritation at the site of implantation.

[0032] FIG. 4 illustrates an alternative stent wire 30. The stent is formed of elongated particles 32, i.e., filaments and fibers. When generally spherically-shaped particles of metal are used to compose sintered metal, the resultant porosity typically is in the range of five to thirty percent. When the particles are elongated, these filaments or fibers can result in a porosity of greater than thirty percent when sintered. The technique of fabricating a stent with elongated filaments or fibers is similar to the method described above for spherical particles or powders. The filaments or fibers are molded and pressurized. Then the fibers are heated to a temperature just below the melting point of the metal.

[0033] A stent made of metal filaments or fibers 32 rather than spherical particles (such as those illustrated in FIG. 2) exhibits greater porosity because of the irregular shape of the particles. The particles can be packed less densely than uniformly-shaped particles but contact between the irregularly-shaped particles nevertheless can be maintained to allow sintering. Thus, the void space or pores 34 in the sintered metal tend to be larger than the pores 18 that result from spherical particle sintering.

[0034] The strength of a stent wire 30 using filaments in FIG. 4 is improved because, upon sintering, the individual strands have a greater surface-area-to-volume ratio and will contact more neighboring strands than will spherical particles. Thus, each filament or fiber will have a greater surface area on which to bond with adjacent filaments or fibers. A matrix of overlapping filaments or fibers thus is formed exhibiting greater porosity and stronger inter-particle bonding.

[0035] Alternatively, wire fibers 36 are woven or

twined into a structure 38 as illustrated in FIG. 5. The individual strands cooperate in a synergistic manner to reinforce the strength of the wire. Additionally, the wire fibers can be woven into the form of a sintered metal sheet having improved and reinforced strength or into a sintered metal tube. Other combinations of particle size and shape can be employed to form a stent wire having different characteristics.

[0036] Alternatively, as illustrated in FIG. 6, the stent wire 42 is formed of an inner core 44 and an outer layer 46 of sintered particles. The outer layer is formed from particles having a different diameter than the diameter of the particles that form the inner core. For example, the core of the metal is formed of particles that have a diameter in the range of 10-20 microns. Surrounding the core are particles that have a diameter in the range of 2-4 microns. The larger particles create a core having larger pores 52. This results in higher porosity and thus a higher load capacity. The smaller particles on the outer layer form smaller pores 54 which reduce the rate of diffusion of drugs into the tissue of the vessel.

[0037] When a therapeutic agent is loaded into a stent formed of the stent wire 42 illustrated in FIG. 6, a larger volume can be stored in the larger pores 52 at the core 44 of the stent wire. Once the stent is placed into the vessel, the therapeutic agent in the stent wire is delivered at a rate that is determined by the smaller pores 54 in the outer layer 46 of the stent wire. Such a structure is expected to be capable of storing a large amount of therapeutic agent at the core and of delivering the therapeutic agent at a slower rate than would be accomplished if the pores of the stent wire were of more uniform size. Consequently, this design is appropriate when long-term drug therapy at a low dosage rate is desired.

[0038] Alternatively, as shown in FIG. 7, a stent wire 56 is formed from sintered particles 58. The pores 62 formed between the sintered metal particle surrounding the solid core retain the therapeutic agent. The overall porosity of a stent having a solid core and porous outer layer is much less than that of a stent wire having similar proportions but which is composed entirely of sintered particles. However, the solid core reinforces the tensile strength and elasticity of the metal stent and is considerably stronger than a uniform-particle sintered stent. Thus, it is desirable to use a sintered stent with a solid core for applications where maximum tensile strength and elasticity is desirable and only a relatively small amount of therapeutic agent is needed.

[0039] The sintered metal stent of still another arrangement can be made of material formed in the spherically-shaped or filament-like particles discussed previously. For example, the stent can be formed of a sheet of sintered metal 64 as shown in FIG. 8 or of a sintered metal tube. By way of example, metal particles 66 are arranged and pressurized into a sheet. The sheet then is heated to a temperature below the melting point of the particles as described previously. The sheet of sintered

metal is porous and has a plurality of pores 68.

[0040] The same principles that apply to porosity and pore size of a wire apply equally to a sintered stent that is formed into a sheet or tube. The advantage of forming the stent from a sheet of metal is that the stent is radially expandable without placing a great deal of strain on the metal lattice when it is expanded. A sheet or tube of sintered metal can be cut in the desired shape to form the metal structural member with a laser, such as a continuous CO₂ laser, a pulsed YAG laser, or an excimer laser, for example, or alternatively, by chemical etching or stamping. When cut from a flat sheet, the stent then is rolled into a cylindrical configuration and is laser welded along the longitudinal edges.

[0041] The stent can be formed into a particular pattern known in the art for stents formed from metal sheets. One such pattern is a rolled locking design and is illustrated in FIG. 9. The sheet is etched into a stent configuration 70 that has a head portion 72 that includes one or more slots 74 for receipt of a number of tail sections 76 that correspond to each slot. The tail sections are received into the slots so as to form a cylindrical loop. Each tail section includes a plurality of teeth 78 that are adapted to cooperatively engage the slot of the head portion. When the teeth engage the slot, the tail sections are retained in place, holding the stent configuration in an expanded state. Additionally, holes 80 are formed throughout the stent to reduce the metal-to-air ratio of the stent. The less metal that is in contact with the wall 14 of the vessel 16, the more likely the stent is to be compatible with the blood.

[0042] Prior to deployment, the tail sections are coiled into a retracted position in a "jelly-roll" fashion. Each tail section then is threaded through each corresponding slot and wound. The stent configuration is expanded by a balloon according to principles that are well known in the art for delivering and implanting stents. As the stent configuration 70 is expanded by a balloon during deployment, it unwinds and the teeth 78 lock into the slots 74 at a desired radial diameter to prevent the stent from returning to its original, retracted state.

[0043] A benefit of the coiled stent shown in FIG. 9 is that the stent 70 can be etched to have a minimal surface area that comes in contact with the walls of the vessel. This may be an important feature when it is desired to cover the entire area of the walls of a blood vessel with a therapeutic agent because the coiled sheet metal stent can be configured to maintain maximum surface area contact with the wall of the blood vessel in contrast to wire stents.

[0044] With reference to FIG. 10, another arrangement a sheet that has particles that are sintered to both sides 84 and 86 of a metal sheet 82. The stent of FIG. 10 is similar in structure to the stent wire of FIG. 7 in that it has a solid core and particles sintered to the core forming a porous outer layer. The solid core reinforces the strength of the metal. The metal sheet also provides a barrier through which a therapeutic agent cannot pass.

Thus, a therapeutic agent loaded into the pores 92 on the top side 84 of the sheet permeates in a first direction 88 outward from the solid core. A therapeutic agent loaded into the pores 94 on the bottom side 86 of the solid wire permeates only in a second direction 90 which is opposite to the direction of the therapeutic agent loaded into the pores on the top side.

[0045] When a stent as shown in FIG. 10 is looped into a cylindrical formation and placed into a vessel, only the top side 84, which is directed radially outward, engages the walls of the vessel. The bottom side 86 faces radially inward and does not come in contact with the walls of the vessel. Thus, if it is desired, a first therapeutic agent can be loaded into the top side to treat the tissue in the wall of the vessel. A second therapeutic agent can be loaded into the bottom side to prevent coagulation of the blood flowing in the vessel. Additionally, the stent can be formed so that particles are sintered only to one side of the stent. A therapeutic agent is loaded into the sintered metal on the porous side of the stent. When a stent is formed with only one porous side, that side can be oriented radially outward to deliver a therapeutic agent to the tissue in the wall of the stent.

[0046] FIG. 11 illustrates a cross-sectional view of a stent wire according to another arrangement. The sheet has a plurality of porous cavities or pores 98. A therapeutic agent is loaded into the pores of the sintered metal. Then, a coating 100 is applied to the sintered metal. The coating may be used for several purposes as described hereinafter.

[0047] With reference to FIG. 12, another arrangement is shown wherein the stent is formed of a sintered sheet 104 of metal having core 106 formed of larger-diameter particles 108 that form larger pores as a result of sintering. The core layer 106 is sandwiched between two layers 110 and 112 formed of smaller-diameter particles 114 or particles that result in the formation of smaller pores. Such a sheet is formed by orienting the middle or core layer 106 of larger-diameter particles 108 along a plane. A top layer of the smaller-diameter particles is arranged in a plane parallel to and above the core layer. A bottom layer of particles are arranged in a plane parallel to and below the core layer. The three layers then are pressed together and sintered into a single sheet. The sheet then can be cut or etched into a stent configuration.

[0048] According to an embodiment of the present invention a coating is applied after a therapeutic agent has been loaded into the pores of the sintered metal. When a therapeutic agent is loaded into the pores of the stent and also into a polymeric coating, the profile of the polymeric coating can be reduced. When such a polymeric coating is applied, a larger dosage of a therapeutic agent can be delivered to the site of stent implantation. Additional benefits can be obtained by loading a stent with a therapeutic agent in the pores of the metal and by then further applying a polymeric coating to the stent. If a polymeric coating is applied to the stent of the

present invention, the principles of reducing profile and reinforcing the stent are realizable because a greater volume of therapeutic agent can be delivered by a polymeric-coated sintered stent than by a coated, all-polymeric stent with comparable dimensions.

[0049] The polymeric material that coats a sintered metal stent preferably comprises a biodegradable, bioabsorbable polymeric film that is capable of being loaded with and subsequently releasing therapeutic drugs. The polymeric coatings preferably include, but are not limited to, polycaprolactone (PCL), poly-DL-lactic acid (DL-PLA) and poly-L-lactic acid (L-PLA) or lactide. Other biodegradable, bioabsorbable polymers such as polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes also may be suitable, and other non-degradable polymers capable of carrying and delivering therapeutic drugs might be appropriate as well. Examples of non-degradable synthetic polymers are those sold under the trade names "Parylene" and "Parylast" by Advanced Surface Technology of Billerica, MA, polyurethane, polyethylene, polyethylene terephthalate, ethylene vinyl acetate, silicone and polyethylene oxide (PEO). The polymeric layer, according to one embodiment, is loaded with a pharmacologic agent for use in localized drug therapy. As used in this description, the terms biodegradable, bioabsorbable, reabsorbable, degradable, and absorbable collectively are meant to encompass materials that are broken down and gradually absorbed or eliminated by the body, whether these processes are due to hydrolysis, metabolic processes, or to bulk or surface erosion. In each of the foregoing embodiments, one polymeric layer preferably is about 0.051 millimeters (0.002 inches) thick.

[0050] The thin polymeric films used to coat the stent preferably first are intermixed with the drug or drugs to be delivered, and then typically are laminated or solvent cast to the surface of the metal structural member. Lamination processing methods and temperatures can vary widely depending on the polymers used and the temperature sensitivity of the loaded drugs. Alternatively, the metal structure of the stent can be encapsulated in the layers of polymeric material by solvent casting, melt processing, insert molding, and dip coating.

[0051] In one arrangement, the membrane is bioabsorbable, but no therapeutic agent is loaded into the polymer. The coating dissolves after implantation and this delays the time that a therapeutic agent is released into the vasculature of a patient. The thickness of the coating, as well as the rate at which the coating is bioabsorbed, determine the length of time that the stent is positioned in the vascular before a therapeutic agent is delivered from the pores of the stent. In another embodiment of the present invention a therapeutic agent can be loaded into the bioabsorbable coating. Thus a therapeutic agent will be delivered to the stent at a rate determined by the bioabsorbability of the coating. Once the bioabsorbable material has completely dissolved, the therapeutic agent in the pores can be delivered at a rate

determined by the pore size and porosity.

[0052] In another embodiment, it is preferred that the coating is permeable and non-absorbable. In such circumstances, the rate at which the drugs permeate into the tissue is controlled by the physical properties of the particular coating selected. Additionally, the coating may be selected to reduce restenosis, thrombosis or other tissue inflammation. For example, a heparin coating is known in the art to reduce blood clotting. Heparin, when coated on a stent, reduces clotting of blood on the surface of the stent. The heparin coating is affixed to the surface of the stent through ionic bonding, end-point attaching, or by photo-linking the heparin.

[0053] In yet another embodiment, a first therapeutic agent is loaded into the coating and a second therapeutic agent is loaded into the pores of the stent. This may be the case when a series of drug dosages or concentrations are needed. When such a stent is placed into the vasculature, the first therapeutic agent is absorbed first by the stent and a second therapeutic agent is absorbed later by the vasculature. This variation adds a further dimension to drug treatment allowing for sequential drug therapy at the site of placement of a stent.

[0054] It will be apparent from the foregoing that while particular forms of the invention have been illustrated and described, various modifications can be made without departing from the scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

Claims

1. A medicated stent, comprising:

- a metallic stent (12) configured to maintain patency of a human vessel, the stent having a plurality of pores (18);
- a therapeutic medication loaded into the pores (18) of the metallic stent;

characterised in that said stent further comprises;

a polymeric coating over the surface of the stent wherein the medication in the pores of the stent is a first medication and wherein the coating contains a second medication.

2. The stent of claim 1, wherein the coating is approximately in the range of 0.00254 mm to 0.051 mm (0.0001 inches to 0.002 inches) thick.
3. The stent of claim 1, wherein the coating is of the group comprising a bio-polymer, a synthetic polymer, a hydrogel, a heparin coating, an ionic heparin coating that is ionic bonded, an end-point attached heparin coating, and a photolinked heparin coating.

4. The stent of claim 3, wherein the coating is of the group comprising polylactic acid, fibrin, polyurethane, polyethylene terephthalate, polyethylene, ethylene vinyl acetate, silicone or polyethylene oxide (PEO). 5
5. The stent of claim 1, wherein the coating is porous and the pores are sized to permit controlled release of the medication through the pores. 10
6. The stent of claim 1, wherein the coating is capable of being dissolved by the body fluids. 15
7. The stent of claim 1, wherein the coating is configured to reduce the porosity of the stent. 20
8. The stent of claim 1, wherein the coating is configured to improve the blood compatibility of the stent. 25
9. The stent of claim 1, wherein the first medication is an antithrombogenic material. 30
10. The stent of claim 9, wherein the first medication is of the group comprising heparin, ticlopidine, coumadin, dipyridamole, aspirin, forskolin. 35
11. The stent of claim 9, wherein the first medication is of the group comprising an GPII_b/III_a blocker, an anti-coagulant, an anti-fibrin agent, an anti-thrombin agent, an anti-platelet agent, an anti-proliferative agent, a radioactive material, a vaso-active drug, and an anti-inflammatory agent. 40
12. The stent of claim 9, wherein the medication promotes endothelialization. 45
13. The stent of any preceding claim, wherein the stent is formed of one of a group selected from a porous metal wire, a sintered stainless steel, a sintered elemental metal, a sintered noble metal, a sintered refractory metal, and a sintered metal alloy. 50
14. The stent of claim 13, wherein the stent is formed of one of a group selected from a shape-memory alloy, a platinum alloy, and a gold alloy. 55
15. The stent of claim 1, wherein the pores are approximately sized within the range of 0.01 microns to 20 microns.
16. The stent of claim 1, wherein the stent is formed of generally spherical particles that are sintered.
17. The stent of claim 16, wherein the sintered particles are approximately .02 microns to 20 microns in diameter.
18. The stent of claim 1, wherein the stent is formed of

metal fibers.

19. The stent of claim 18, wherein the metallic fibers are woven.
20. The stent of claim 1, wherein the stent has an inner layer of particles and an outer layer of particles, the outer layer of particles have a larger diameter than the inner layer of particles.
21. The stent of claim 1, wherein the stent has a non-porous core and has a porous metal coating over the non-porous core.
22. The stent of claim 6, wherein the stent is generally tubular and has a surface that is configured to be embedded into the walls of the vessel, wherein the stent is proportioned to maximize the area of the surface while allowing efficient endothelialization of the stent.
23. The stent of claim 1, wherein the stent is configured to be expandable beyond the elastic limit of the stent by a balloon.
24. The stent of claim 1, wherein the stent is configured to be self-expanding.
25. The stent of claim 1, wherein the stent is configured to be deployed in one of a group selected from a blood vessel, an esophagus, and a biliary duct.

Patentansprüche

1. Medizinisch behandelter Stent, umfassend: einen metallischen Stent (12), konfiguriert, um die Integrität eines humanen Gefäßes aufrechtzuerhalten, wobei der Stent mehrere Poren (18) aufweist; eine therapeutische Medikation, die in den Poren (18) des metallischen Stents aufgenommen ist; **dadurch gekennzeichnet, dass** der Stent weiterhin umfasst; eine polymere Beschichtung über der Oberfläche des Stents, worin die Medikation in den Poren des Stents eine erste Medikation ist und worin die Beschichtung eine zweite Medikation enthält.
2. Stent nach Anspruch 1, worin die Beschichtung ungefähr im Bereich von 0,00254 mm bis 0,051 mm (0,0001 Zoll bis 0,002 Zoll) dick ist.
3. Stent nach Anspruch 1, worin die Beschichtung aus der Gruppe besteht, umfassend ein Biopolymer, ein synthetisches Polymer, ein Hydrogel, eine Heparinbeschichtung, eine ionische Heparinbeschichtung, die ionisch gebunden ist, eine Endpunkt-gebundene Heparinbeschichtung und eine photogebundene Heparinbeschichtung.

4. Stent nach Anspruch 3, worin die Beschichtung aus der Gruppe ist, umfassend Polymilchsäure, Fibrin, Polyurethan, Polyethylenterephthalat, Polyethylen, Ethylenvinylacetat, Silikon oder Polyethylenoxid (PEO). 5
 5. Stent nach Anspruch 1, worin die Beschichtung porös ist und die Poren so bemessen sind, dass sie kontrollierte Freisetzung der Medikation durch die Poren erlauben. 10
 6. Stent nach Anspruch 1, worin die Beschichtung durch Körperfluide gelöst werden kann.
 7. Stent nach Anspruch 1, worin die Beschichtung konfiguriert ist, um die Porosität des Stents zu verringern. 15
 8. Stent nach Anspruch 1, worin die Beschichtung konfiguriert ist, um die Blutkompatibilität des Stents zu verbessern. 20
 9. Stent nach Anspruch 1, worin die erste Medikation ein antithrombogenes Material ist. 25
 10. Stent nach Anspruch 9, worin die erste Medikation aus der Gruppe ist, umfassend Heparin, Ticlopidin, Coumadin, Dipyridamol, Aspirin, Forskolin.
 11. Stent nach Anspruch 9, worin die erste Medikation aus der Gruppe ist, umfassend einen GPII_bIII_a-Blocker, ein Anticoagulanz, ein Antifibrinmittel, ein Antithrombinmittel, ein Antiplättchenmittel, ein Antiproliferationsmittel, ein radioaktives Material, einen vaso-aktiven Wirkstoff und ein entzündungshemmendes Mittel. 30
 12. Stent nach Anspruch 9, worin die Medikation Endothelialisierung fördert. 40
 13. Stent nach einem der vorhergehenden Ansprüche, worin der Stent gebildet ist aus einer Gruppe, ausgewählt aus einem porösen Metalldraht, einem gesinterten Edelstahl, einem gesinterten elementaren Metall, einem gesinterten Edelmetall, einem gesinterten schwer schmelzbaren Metall und einer gesinterten Metalllegierung. 45
 14. Stent nach Anspruch 13, worin der Stent gebildet ist aus einem aus einer Gruppe, ausgewählt aus einer Memory-Legierung, Platinlegierung und einer Goldlegierung. 50
 15. Stent nach Anspruch 1, worin die Poren eine ungefähre Größe aufweisen, die innerhalb des Bereichs von 0,01 Mikrometer bis 20 Mikrometer liegt. 55
 16. Stent nach Anspruch 1, worin der Stent aus im Wesentlichen sphärischen Teilchen gebildet ist, die gesintert sind.
 17. Stent nach Anspruch 16, worin die gesinterten Teilchen ungefähr 0,02 Mikrometer bis 20 Mikrometer Durchmesser aufweisen.
 18. Stent nach Anspruch 1, worin der Stent aus Metallfasern gebildet ist.
 19. Stent nach Anspruch 18, worin die Metallfasern gewoben sind.
 20. Stent nach Anspruch 1, worin der Stent eine innere Schicht aus Teilchen und eine äußere Schicht aus Teilchen aufweist, wobei die äußere Teilchenschicht einen größeren Durchmesser als die innere Teilchenschicht aufweist.
 21. Stent nach Anspruch 1, worin der Stent einen nichtporösen Kern aufweist und eine poröse Metallbeschichtung über den nichtporösen Kern besitzt.
 22. Stent nach Anspruch 6, worin der Stent im Allgemeinen röhrenförmig ist und eine Oberfläche aufweist, die konfiguriert ist, um in die Wände des Gefäßes eingebettet zu werden, worin der Stent so proportioniert ist, um die Oberfläche zu maximieren während wirkungsvolle Endothelialisierung des Stents erlaubt wird.
 23. Stent nach Anspruch 1, worin der Stent so konfiguriert ist, dass er über das elastische Limit des Stents durch einen Ballon expandierbar ist.
 24. Stent nach Anspruch 1, worin der Stent selbstexpandierend ausgestaltet ist.
 25. Stent nach Anspruch 1, worin der Stent so ausgestaltet ist, dass er in einem aus einer Gruppe, ausgewählt aus einem Blutgefäß, einem Ösophagus und einem Gallengang, eingesetzt werden kann.
- Revendications**
1. Stent renfermant des substances actives, comprenant :

un stent métallique (12) configuré de manière à maintenir la perméabilité d'un vaisseau humain, le stent ayant une pluralité de pores (18) ; une médication thérapeutique chargée dans les pores (18) du stent métallique ;

caractérisé en ce que ledit stent comprend en outre ;

- un revêtement polymérique sur la surface du stent dans lequel la médication dans les pores du stent est une première médication et dans lequel le revêtement contient une seconde médication.
2. Stent selon la revendication 1, dans lequel le revêtement est approximativement dans la gamme de 0,00254 mm à 0,051 mm (0,0001 pouces à 0,002 pouces) d'épaisseur.
 3. Stent selon la revendication 1, dans lequel le revêtement provient du groupe comprenant un biopolymère, un polymère synthétique, un hydrogel, un revêtement d'héparine, un revêtement d'héparine ionique qui est lié de manière ionique, un revêtement d'héparine fixé au point terminal, et un revêtement d'héparine photolié.
 4. Stent selon la revendication 3, dans lequel le revêtement provient du groupe comprenant l'acide polylactique, la fibrine, le polyuréthane, le téréphtalate de polyéthylène, le polyéthylène, l'éthylène-acétate de vinyle, la silicone ou l'oxyde de polyéthylène (PEO).
 5. Stent selon la revendication 1, dans lequel le revêtement est poreux et les pores sont calibrés pour permettre une libération contrôlée de la médication au travers des pores.
 6. Stent selon la revendication 1, dans lequel le revêtement est capable d'être dissous par les liquides organiques.
 7. Stent selon la revendication 1, dans lequel le revêtement est configuré de manière à réduire la porosité du stent.
 8. Stent selon la revendication 1, dans lequel le revêtement est configuré de manière à améliorer la compatibilité sanguine de la prothèse.
 9. Stent selon la revendication 1, dans lequel la première médication est un matériau antithrombogène.
 10. Stent selon la revendication 9, dans lequel la première médication provient du groupe comprenant de l'héparine, de la ticlopidine, de la coumadine, du dipyridamole, de l'aspirine, de la forskoline.
 11. Stent selon la revendication 9, dans lequel la première médication provient du groupe comprenant un inhibiteur de GPIIb/IIIa, un anticoagulant, un agent anti-fibrine, un agent anti-thrombine, un agent anti-plaquettaire, un agent anti-proliférant, un matériau radioactif, un médicament vasomoteur et
- un agent anti-inflammatoire.
12. Stent selon la revendication 9, dans lequel la médication favorise l'endothélialisation.
 13. Stent selon l'une quelconque des revendications précédentes, dans lequel la prothèse est formée de l'un des éléments du groupe sélectionné parmi un fil métallique poreux, de l'acier inoxydable fritté, un élément métal fritté, un métal noble fritté, un métal réfractaire fritté, et un alliage de métal fritté.
 14. Stent selon la revendication 13, dans lequel le stent est formé d'un élément du groupe sélectionné parmi un alliage à mémoire de forme, un alliage de platine, et un alliage d'or.
 15. Stent selon la revendication 1, dans lequel les pores sont approximativement calibrés dans la gamme de 0,01 microns à 20 microns.
 16. Stent selon la revendication 1, dans lequel le stent est formé de particules généralement sphériques qui sont frittées.
 17. Stent selon la revendication 16, dans lequel les particules frittées sont approximativement de 0,02 microns à 20 microns de diamètre.
 18. Stent selon la revendication 1, dans lequel le stent est formé de fibres métalliques.
 19. Stent selon la revendication 18, dans lequel les fibres métalliques sont tissées.
 20. Stent selon la revendication 1, dans lequel le stent a une couche interne de particules et une couche externe de particules, la couche externe de particules a un diamètre plus grand que la couche interne de particules.
 21. Stent selon la revendication 1, dans lequel le stent a un coeur non poreux et un revêtement métallique poreux sur le coeur non poreux.
 22. Stent selon la revendication 6, dans lequel le stent est généralement tubulaire et a une surface qui est configurée de manière à être incluse dans les parois du vaisseau, dans lequel le stent est proportionné de manière à maximiser la zone de la surface tout en permettant une endothélialisation efficace du stent.
 23. Stent selon la revendication 1, dans lequel le stent est configuré de manière à ce qu'il soit extensible au-delà de la limite élastique du stent par un ballon.
 24. Stent selon la revendication 1, dans lequel le stent

est configuré pour être auto extensible.

- 25.** Stent selon la revendication 1, dans lequel le stent est configuré pour être déployé dans un élément du groupe sélectionné parmi un vaisseau sanguin, un oesophage et un canal biliaire.

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FIG. 1

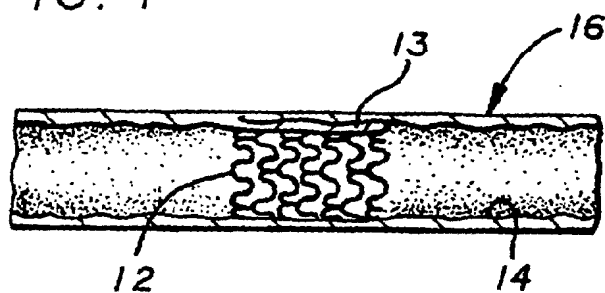


FIG. 2

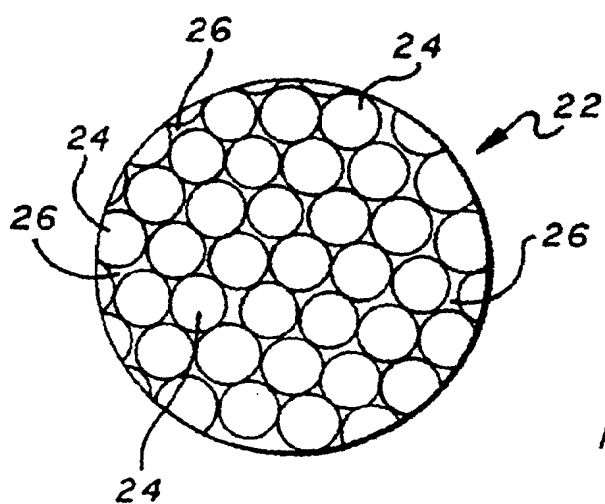
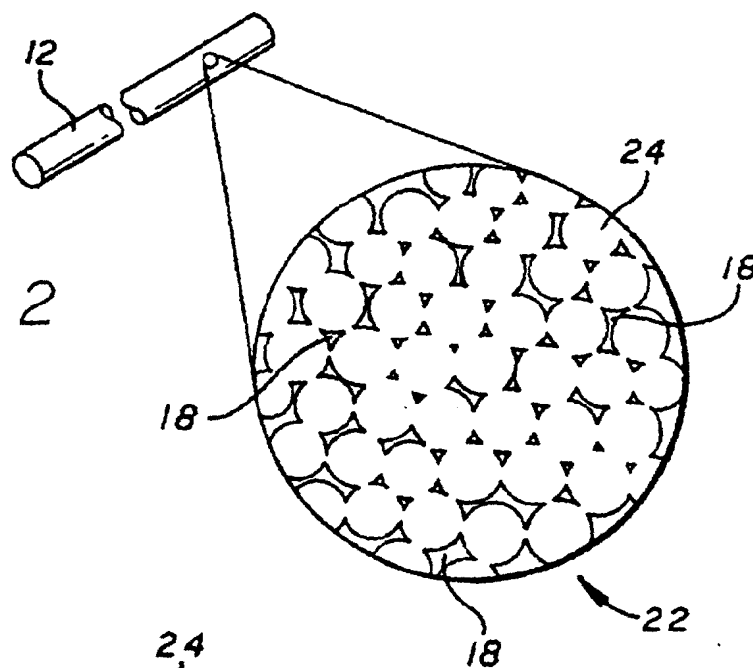


FIG. 3

FIG. 5

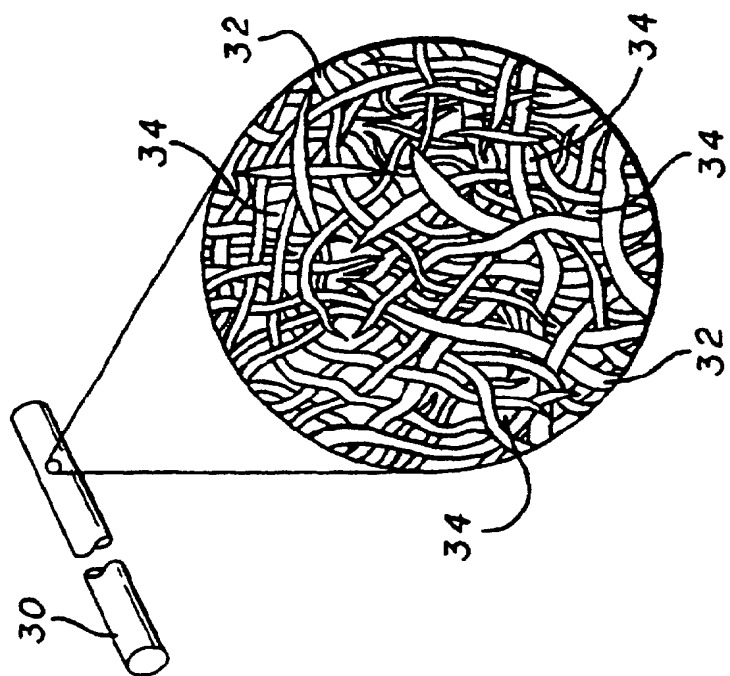
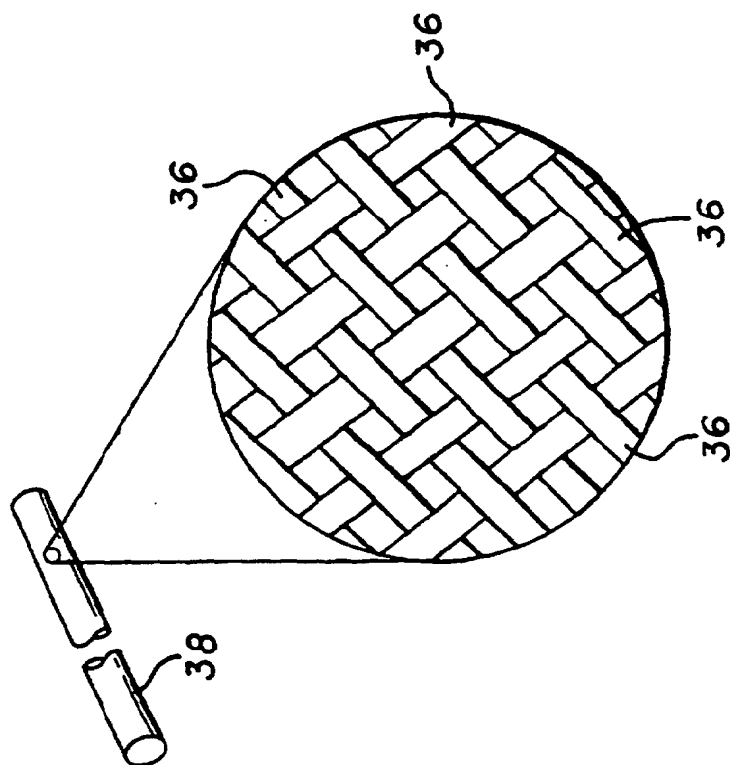


FIG. 4

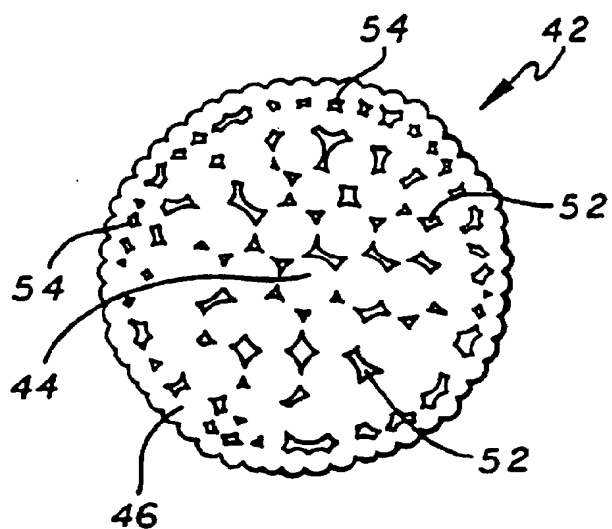


FIG. 6

FIG. 7

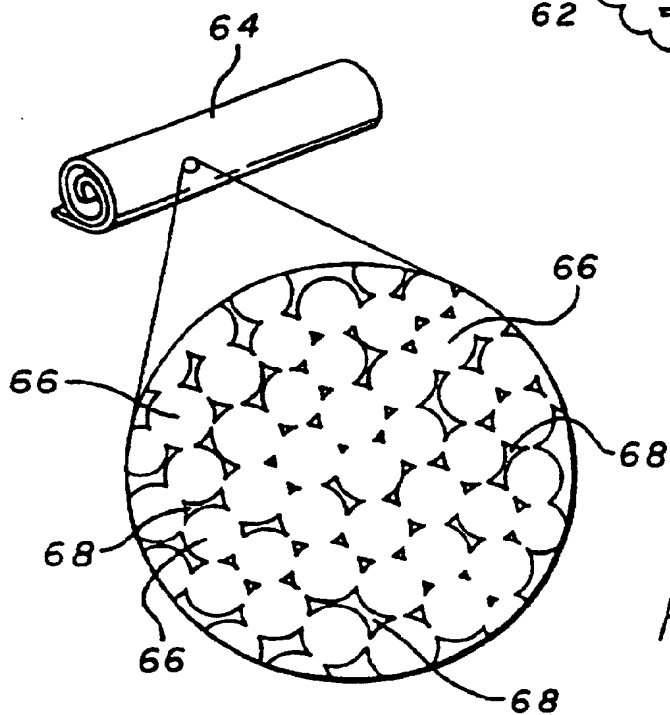
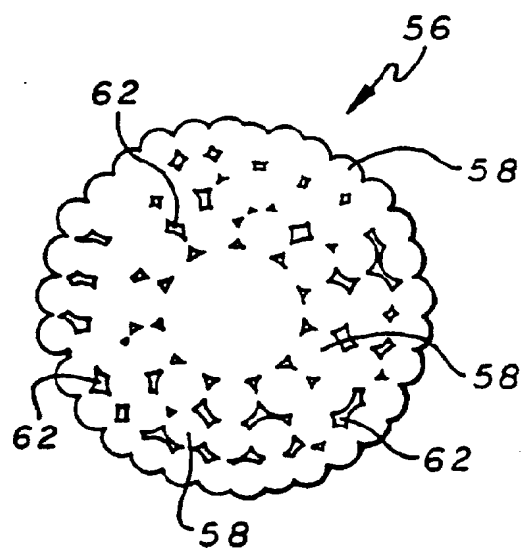


FIG. 8

FIG. 9

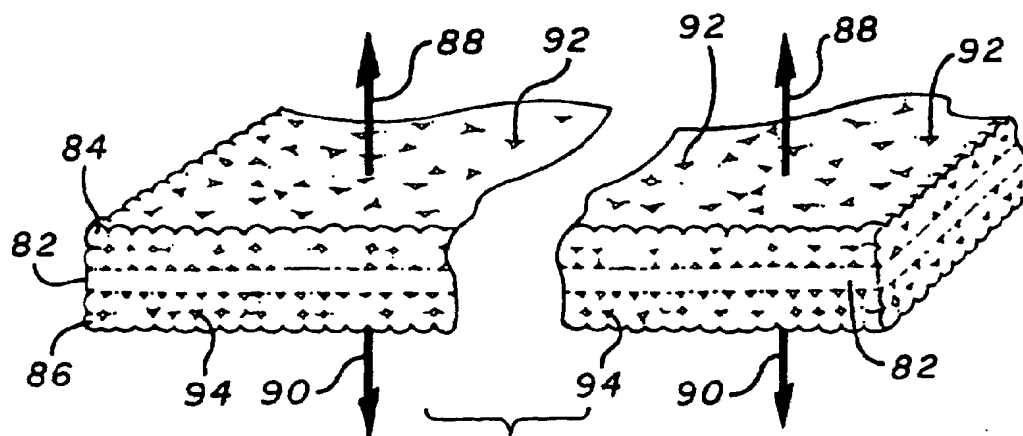
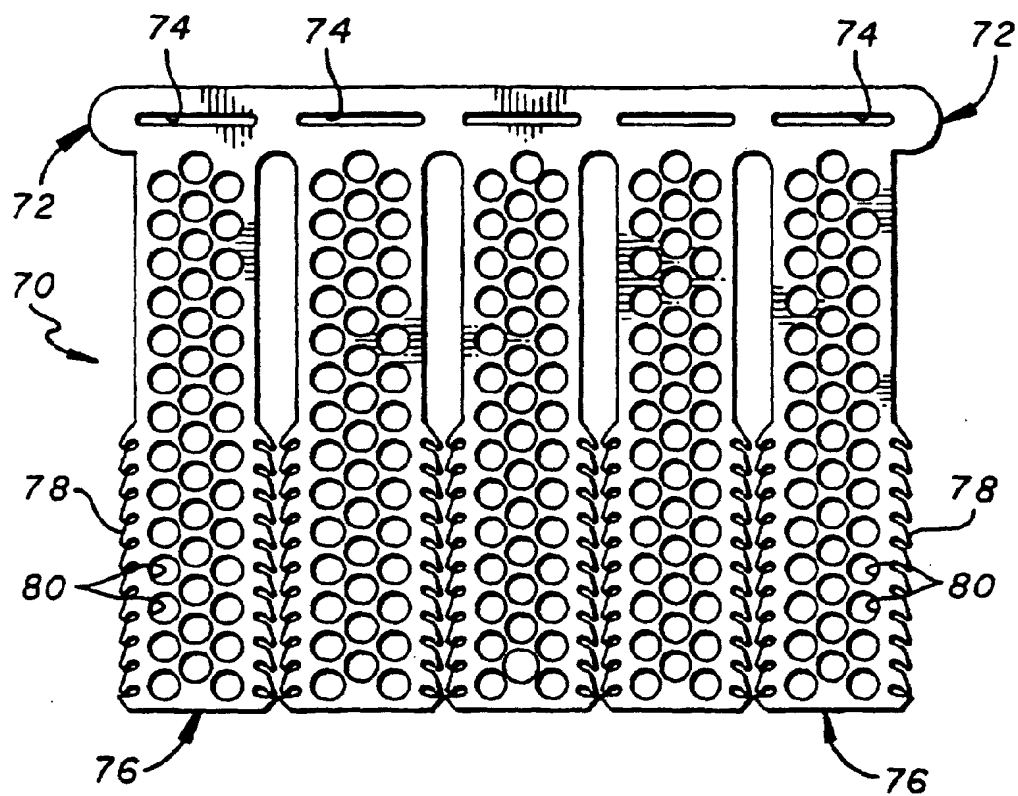


FIG. 10

FIG. 11

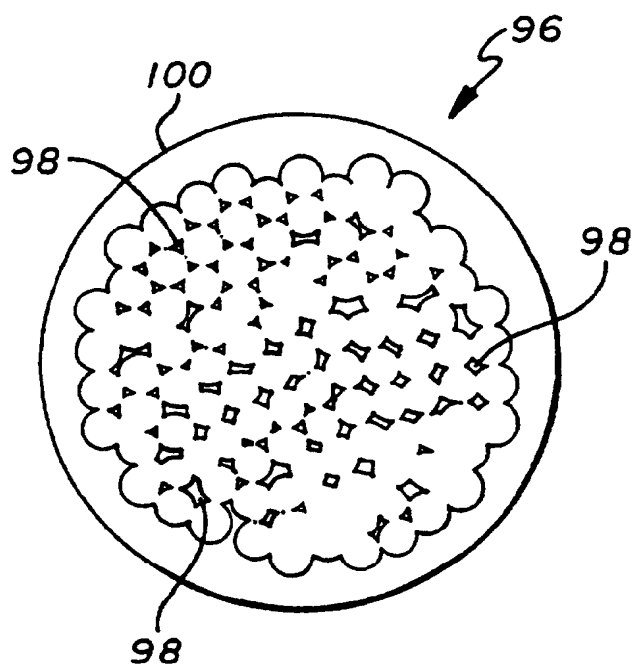
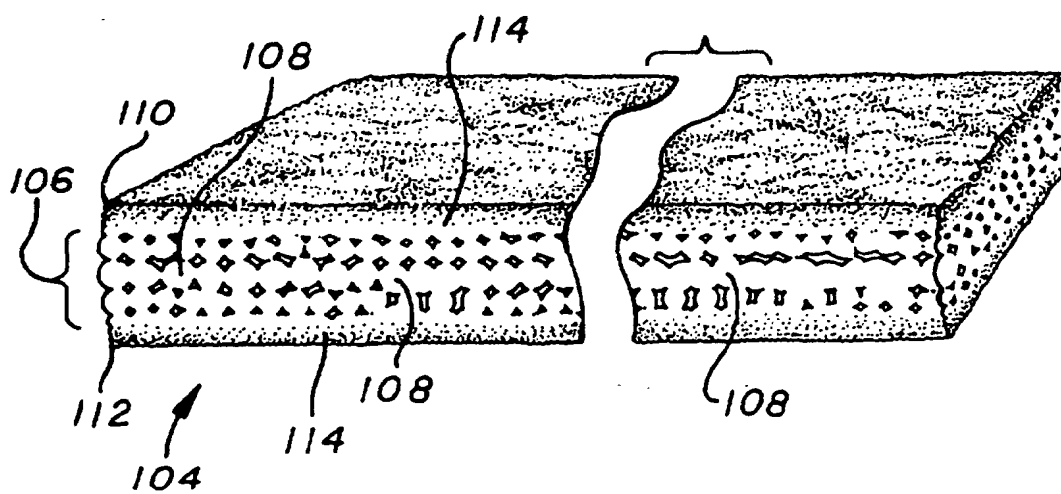


FIG. 12





(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
30.08.2000 Bulletin 2000/35

(51) Int Cl.7: **A61F 2/06, A61L 31/00**

(43) Date of publication A2:
04.11.1998 Bulletin 1998/45

(21) Application number: **98302905.9**

(22) Date of filing: **15.04.1998**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
 Designated Extension States:
AL LT LV MK RO SI

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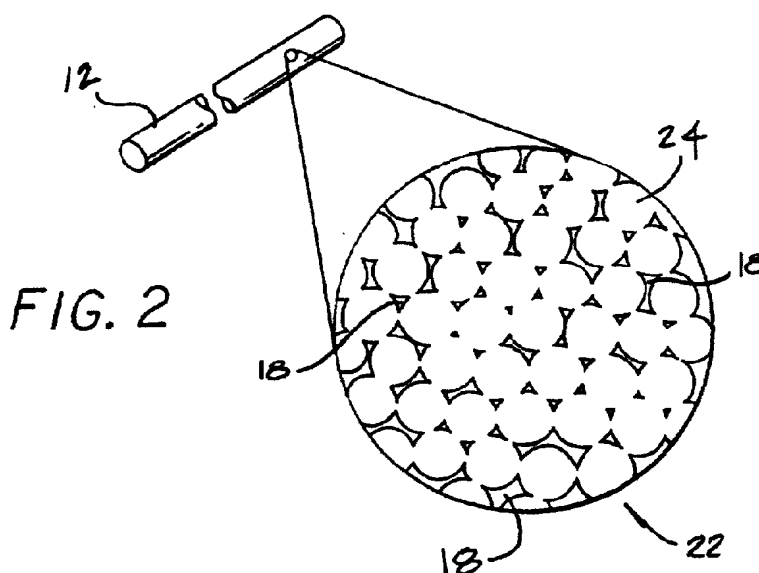
(30) Priority: **15.04.1997 US 842660**

(71) Applicant: **Advanced Cardiovascular Systems, Inc.**
Santa Clara, CA 95054-8167 (US)

(54) **Porous medicated stent**

(57) A medicated prosthesis, such as a stent, is deployed in a human vessel. A metallic stent has a plurality of pores in the metal which are loaded with medication. When the stent is implanted into the vasculature of a patient, the medication in the stent dissipates into the tissue of the vasculature proximate the stent. The stent may be formed from a porous metal in the form of a wire,

tube, or metal sheet. The present invention also includes a method of treating vasculature disease by delivering medication to the site of the vascular disease including the step of deploying a metal stent having a plurality of pores in the stent and further having medication in the pores and delivering the stent to the site of vasculature disease.





European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 98 30 2905

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			A61L A61F
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 6 July 2000	Examiner Thornton, S
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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